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EXAMINER
MEHTA, ASHWIN D

ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,054	LAM, ERIC	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5062002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The priority statement on lines 1-4 of page 1 of the specification should be amended to indicate that the instant application is the U.S. national stage of PCT/US00/15783, filed 08 June 2000, which claims priority to U.S. Provisional Application 60/138,968, filed 11 June 1999.

Claim Objections

2. Claims 25, 29, and 30 are objected to for the following reasons:

Claims 25 is objected to because of the following informalities: In line 4 of part b), the recitation, "of claim 24" should be deleted, as part a) already indicates that the claim is dependent on claim 24. Appropriate correction is required.

Claim 29 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). In the interest of compact prosecution, the claim has been interpreted as if the recitation, "of claim 1" in line 3 of part b) was deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1: the claim is indefinite because it does not make clear what the heterologous DNA segment is intended to be. The body of the claim indicates what the construct comprises, including DNA substrates for a transposase, cloning sites disposed between the DNA substrates, positive and negative selection genes, and optionally, a detectable marker gene whose product is no longer detectable following excision of the material between the DNA substrates. However, the only mention of the heterologous DNA is in line 2. The claim does not mention what other genes, for example a gene of interest, are comprised on the DNA construct. The only genes mentioned are the selection and marker genes. It is unclear whether the heterologous DNA segment is supposed to be such a gene of interest, for example, as DNA constructs and vectors are used in the art to introduce genes of interest into cells. It is unclear that the heterologous DNA segment is intended to be the selection and/or marker genes. It is noted that the first and second cloning sites may comprise such a gene of interest. However, after action of the transposase, the cloning sites excise from the genome and, giving the claim its broadest reasonable interpretation, do not necessarily re-insert into the genome.

In claim 24: the recitation, "substantially homologous" in line 7 renders the claim indefinite. It is unclear what distinguishes a DNA sequence that is "substantially homologous" to sequences at the pre-determined location in the genome versus from those that are not substantially homologous.

In claim 29: the claim is indefinite for being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Lines 1 and 2 of the claim indicate that it is drawn to a method for activation tagging of a plant genome to create variants displaying a desired phenotype. However, no step indicates when the activation tagging takes place. The specification indicates that activation tagging comprises inserting DNA into genome wherein the DNA comprises promoters that transactivate the expression of genes in the vicinity of the insertion (paragraph bridging pages 4-5). However, none of the recited steps in claim 29, nor claims 1 and 24, from which claim 29 depends, make any mention of any such promoter that activates expression of genes in the genome.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 24-32 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA construct for integration of heterologous DNA segment into genomes, wherein the DNA construct is adapted for integrating a heterologous DNA segment at a pre-determined location in the Chlamydomonas genome, and a method for inserting a heterologous DNA molecule into a pre-determined location of a Chlamydomonas genome, does not reasonably provide enablement for DNA constructs adapted for integrating a heterologous DNA segment into pre-determined locations of other plant genomes, or methods for inserting a heterologous DNA into a pre-determined location in other plant genomes, or a method of

activation tagging of a plant genome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn towards a DNA construct for integration of a heterologous DNA segment into any genome, wherein the DNA construct is adapted for integrating a heterologous DNA segment at a pre-determined location of a genome of any and all cell types; a method for inserting a heterologous DNA molecule into a pre-determined location on any plant genome; a kit for inserting a heterologous DNA molecule into any pre-determined location of any plant genome or for activation tagging, comprising said DNA construct or said DNA construct that is not adapted for integration into a pre-determined location; a method for activation tagging any plant genome to create variants displaying a desired phenotype, comprising transformed plant cells with said DNA construct, or with a DNA construct that is not adapted for integration into a pre-determined location.

The specification provides a prophetic example of a DNA construct, shown in Figure 1, that would comprise the CodA gene, two polylinker sequences, short maize Ds elements (<1.5 kb), a Bar gene, and the GUS coding sequence operably linked to the CaMV 35S promoter. The Ds elements would be positioned next to the right border of the construct and within the 35S-GUS cassette. Frequency of excision of the Ds element, after introduction into a plant genome, would be monitored by loss of GUS activity. The CodA and Bar genes and the polylinkers would be located within the Ds elements. The polylinkers would flank the Bar gene. Unspecified sequences from the Arabidopsis TGA3 gene would be inserted into the polylinkers (page 25). The specification prophetically indicates that the construct would then be introduced

into Arabidopsis via Agrobacterium, and transgenic lines can be selected on PPT-containing plates. The transformed lines would be evaluated by Southern hybridization to select those that contain a single copy of the construct. These would then be selfed to produce homozygous plants, which would be crossed with a transgenic plant homozygous for the maize Ac transposase gene. This would excise the Ds element from the construct, which would then insert by homologous recombination to sites homologous to the TGA3 sequences. If the DNA construct does not contain the TGA3 sequences, or any sequences homologous to genomic sequences, then the excised Ds element would reinsert randomly into the genome (pages 25-26).

A review of claim 24 indicates that it is drawn to a genus of DNA constructs, which comprise targeting inserts that are substantially homologous to sequences present in the genome of any type of cell, the targeting segments enabling the DNA construct to integrate into the genome at the predetermined location by homologous recombination. Variation is expected in the targeting segments of the species of DNA constructs, as they are substantially homologous to sequences within different genomes, requiring homologous recombination to occur at the pre-determined location in different genomes. Claim 25 is directed to a method for inserting a heterologous DNA molecule into a pre-determined location in any plant genome. Claim 29 is directed to a method for activation tagging of any plant genome, comprising transforming plant cells with a DNA construct of claim 24 or claim 1, which does not comprise the targeting segments.

However, the specification does not enable the claimed DNA constructs containing targeting sequences from all plant species. The specification does not enable homologous recombination of heterologous DNA molecules into pre-determined locations in all plants.

Homologous recombination is not known to occur in plant species other than Chlamydomonas. Puchta (Plant Mol. Biol., 2002, Vol. 48, pages 173-182) discusses the state of gene replacement by homologous recombination in plants, and teaches that efficient gene targeting techniques in higher plants have not yet been achieved. Puchta teaches, for example, that improvements to gene targeting in animals have not been successful in plants (page 173), that extending the length of homology in the transferred DNA to up to 22 kb did not result in higher frequencies (page 174). Puchta discusses that results of gene targeting in Arabidopsis, involving the AGL5 MADS-box gene, have been controversial and that no statistically sound conclusion as to the frequencies of targeting could be drawn from this single event (paragraph bridging pages 174-175). Terada et al. (Nature Biotech., 2002, Vol. 20, pages 1030-1034) also address the reports of gene targeting in Arabidopsis, and assert that no one has yet repeated the experiments, and that the authors of one of those reports also detected the occurrence of undesirable events, including ectopic recombination and/or simultaneous ectopic integration of the transgene used (page 1030). While Terada et al. teach a method for homologous recombination in rice, it is noted that this method was not known at the time the instant invention was filed. In the absence of further guidance, undue experimentation would be required to use the claimed DNA constructs comprising targeting sequences that are homologous to genomic sequences from any and all plant species and practice the claimed methods in all plant species. As discussed above, the specification prophetically describes the construction of a vector to be used in a method in which a heterologous DNA is to be inserted by homologous recombination into a pre-determined location. The specification does not teach that the method resulted in the successful insertion of the heterologous DNA into the genome of any plant. The specification does not teach how one

skilled in the art is to overcome the deficiencies of the art. See Genentech, Inc. V. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Further regarding claims 29-32: claim 29 is directed to a method for activation tagging of any plant genome, comprising transforming plant cells with a DNA construct of claim 24 or claim 1. As currently written, it is unclear how one skilled in the art can use the claimed method. The specification in the paragraph bridging pages 4-5 indicates that activation tagging comprises tagging genes randomly by inserting DNA into genomes, wherein the DNA comprises promoters that transactivate the expression of genes in the vicinity of the insertion. However, claim 29 does not mention anything about the essential step of expressing genes in the host genome, or that the DNA construct also comprises promoter that is essential to cause any such transactivation. As these features are essential to activation tagging and are omitted from claim 29, the claim is not enabled. See MPEP 2172.01 and 2164.08(c). Further, as the host plant is likely to have numerous insertions of the DNA construct, it is not clear how one skilled in the art would use the method to select for a desired phenotype. Once transgenic lines comprising the construct and the transposase-encoding line are crossed, the material between the transposes substrates on each copy of the construct present in the genome will be mobilized. Genes near each of the re-insertion sites may be activated. As numerous genes would become activated, it is unpredictable what the effect on the host plant would be, or even if it would be viable. Further, the DNA segment flanked by the transposon substrate sites would continue to "jump," since the transposase is still present in the host plant. In the absense of further guidance, undue experimentation would be require by one skilled in the art to use the claimed method to select for

a desired phenotype. Furthermore, it is unclear how one skilled in the art would use the DNA constructs of claim 24 in the method for activation tagging of claim 29, even if the specification enabled one skilled in the art to insert heterologous DNA into a pre-determined location by homologous recombination in any plant genome. As the heterologous DNA construct would only insert into the pre-determined location, it is unclear, and not explained by the specification, how it would insert randomly into the genome and activate the expression of genes in the genome. See Genentech, Inc. V. Novo Nordisk, A/S, *supra*. Given the breadth of the claims encompassing DNA constructs comprising targeting sequences that are homologous to genomic sequences from any and all plant species, methods requiring homologous recombination events to occur in any and all plant species, and a method for activation tagging using the claimed DNA constructs, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoder et al. (WO 92/01370) in view of Hashimoto et al. (Plant Sci., February 1999, Vol. 141, pages 175-181) and Lloyd et al. (Mol. Gen. Genet., 1994, Vol. 242, pages 653-657).

The claims are broadly drawn towards a DNA construct for integration of a heterologous DNA segment into genomes within any type of cell, the DNA construct comprising termini disposed therebetween: a) a pair of DNA substrates for any transposase, between which comprise i) first and second cloning sites, between which lies a positive selection gene encoding a product that confers resistance to a positive selection agent that is deleterious to cells in which the DNA construct has not integrated and ii) a negative selection gene disposed between one of the DNA substrates for the transposase and one of the two cloning sites, but not between the two cloning sites, wherein the negative selection gene confers renders the cell susceptible to a negative selective agent, wherein cells in which the DNA construct has not integrated are not susceptible to the agent, and optionally b) a detectable marker gene inserted in the DNA construct such that upon excision of the DNA construct from a genome by the action of the transposase, the detectable gene product is no longer detectable.

Yoder et al. teach methods to introduce heterologous DNA into genomes, comprising use of transposon systems. DNA constructs are made that comprise substrate sites recognized by a transposase. DNA within these sites can be from any source and can include selection and marker genes. The substrate sites recognized by the transposase can be from a maize Ds element, which is recognized by the maize Ac transposase. Heterologous genes of interest are included on the construct, and can be included within or outside of the transposase substrate sites. Any selection or marker genes can be used, including that encoding β-glucuronidase and

herbicide resistance genes such as those conferring resistance to phosphinothricin or glyphosate. Any types promoters can be used to express the selection, marker, and heterologous genes, including constitutive and inducible promoters. The DNA construct can be introduced into plants by any means, including via Agrobacterium, in which case the DNA construct would be within borders of Agrobacterium tDNA of a T-DNA vector (pages 6-15, 24-39).

Yoder et al. do not teach the cytosine deaminase (coda) gene.

Hashimoto et al. teach the use of the cytosine deaminase gene as a negative selection marker in plants and assert that it can be used with transposon mobilization studies. The CaMV 35S promoter was used to transcribe the gene in plants. Hashimoto et al. teach that a single gene is sufficient to provide good negative selection (pages 177-180).

Lloyd et al. teach the strategy of using of a recombinase system to remove a DNA segment containing the coding sequence of the GUS marker gene from the genome of plants. Substrate sites for the recombinase were placed between the GUS coding sequence and the CaMV 35S promoter that was operably linked to it. The action of the recombinase removed the GUS coding sequence, but not the promoter (pages 656-657).

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to modify the method of introducing heterologous genes into genomes of Yoder et al. by using any other selection marker genes, such as the cytosine deaminase gene taught by Hashimoto et al. One would have been motivated to do so, given assertion by Hashimoto et al. that it would be in conjunction with transposons. It would have been obvious to place cloning sites anywhere outside of the transposase substrate sites in the construct of Yoder et al., including the termini of the construct, to facilitate introduction of the

gene(s) of interest. It would also have been obvious to place polylinker sites within the transposase substrate sites, to facilitate insertion of further selection, marker, or other heterologous genes. It also would be have been obvious to further modify the DNA construct by inserting a marker gene, such as the GUS gene, within the construct such that a transposase substrate site was in between the promoter and the marker coding sequence, following the strategy used by Lloyd et al. One would have been motivated to do so, given the demonstration by Lloyd et al. that this strategy provides another tool to one of ordinary skill in the art to monitor the excision event following the action of the transposase, as the promoter controlling expression of the marker gene would no longer be operably linked to the coding sequence.

6. Claims 1-32 are rejected.

Contact Information

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. Status information for published applications may be

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September 3, 2004

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